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Slow Brain Potentials in
Occupational Medicine

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THE APPLICATION OF EVENT-RELATED SLOW BRAIN POTENTIALS IN OCCUPATIONAL MEDICINE

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ABSTRACT

Workers exposed to solvents, pesticides, heavy metals and other neurotoxic chemicals frequently exhibit symptoms of mental confusion, impaired attention, and memory loss. These symptoms suggest the impairment of several aspects of cognitive function that can be assessed readily by noninvasive electrophysiological tests. Event-related slow potentials (ERSPs) of the brain constitute a family of scalp-recorded electrophysiological measures of cognitive and/or motor function. Applications of CNV, P300 and other ERSPs, as well as criteria for the selection and evaluation of neurotoxicity tests, in occupational health assessment are discussed.

KEYWORDS

Occupational health, neurotoxicology, event-related slow potentials, CNV, P300.

INTRODUCTION

Workers today are exposed to a growing array of chemicals, some of which are known to produce neurotoxic effects if ingested, inhaled, or absorbed through the skin. In the case of lead poisoning the symptoms of overt neurotoxicity are clearly defined and body burden can be monitored to prevent excessive accumulation of the neurotoxic substance. For other chemicals developed during the past few decades, far less is known about the consequences of worker exposure and biological markers of body burden are seldom available. In the face of these uncertainties, the search continues for more sensitive and reliable methods to detect and characterize the neurobehavioral effects of chemical exposure in the workplace.

The electroencephalogram (EEG) recorded non-invasively from the scalp is a direct measure of CNS function that is used in neurotoxicological assessment. Clinical analysis of spontaneous EEG, however, is a relatively insensitive index of neurotoxicity, particularly when exposure

levels are moderate to light. Several computer-based methods of EEG analysis are available that offer more sophisticated and, presumably, more sensitive measures. Gilioli et al (this volume) describes one of these methods--EEG spectral analysis, and Cosi (this volume) describes another--sensory evoked potential analysis. This paper will review event-related slow potentials (ERSPs) of the brain, a third type of EEG measure that has proven to be useful in assessing the effects of psychoactive drugs (Tecce et al, 1978). The purpose of this paper is to explore the potential utility of ERSs in occupational medicine.

DEFINITION OF EVENT-RELATED POTENTIAL (ERP)

ERPs are electrical responses of the brain to external stimulus events (i.e., auditory, visual, and somatosensory evoked potentials) or electrical signs of internal events (or processes) initiated in the brain. Internal events include efferent motor commands (ergo motor-related potentials) and a broad spectrum of information processing, associative, or cognitive processes that originate in the brain (e.g., association potentials and the expectancy wave). Two general classes of ERPs may be distinguished: exogenous and endogenous. Exogenous potentials are evoked by external stimulus events, while endogenous potentials reflect events or processes that originate in the brain.

If subjects are required to attend, process, or respond to external stimuli in some manner such as selectively counting or button pressing when a particular signal occurs, the resultant waveform will include early (sensory-evoked) exogenous components as well as later (cognitive) endogenous components. The term event-related "slow" potentials refers to

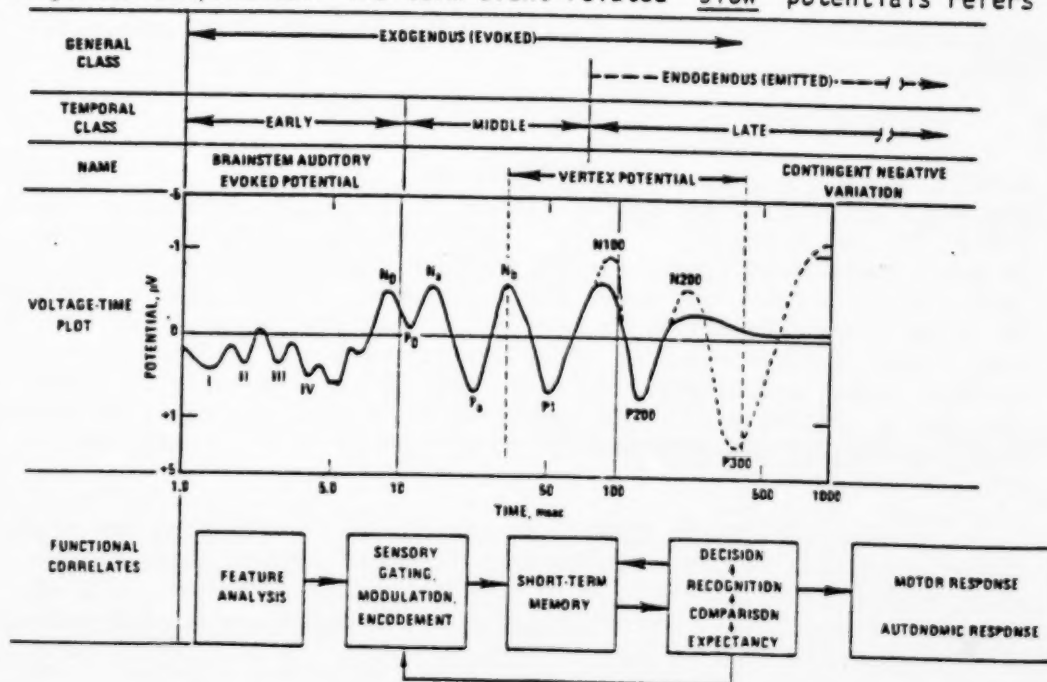


Fig. 1. Temporal and functional characteristics of event-related brain potentials evoked by or emitted in response to a brief auditory click. Functional correlates are hypothetical. (Adapted from

later endogenous components associated with information processing, cognition, and memory. The latency of endogenous potentials is usually 100 msec or more after stimulus onset. Endogenous potentials may persist for several hundred msec, while exogenous components are usually much briefer. Fig. 1 illustrates the temporal and functional characteristics of these two classes of potentials in the auditory modality (cf. Hillyard and Woods, 1979 for an excellent review).

The three most prominent ERSPs are: (1) Contingent Negative Variation (CNV)--a slow vertex-negative shift in scalp-recorded EEG that arises during a signalled reaction-time foreperiod (Walter et al, 1964); (2) Readiness Potential (RP)--a slow vertex-negative shift in EEG baseline that arises about one second prior to a stereotyped movement (Kornhuber and Deecke, 1965); and (3) P300--a large positive wave that peaks 300-600 msec following a stimulus that delivers relevant information to the perceiver (Sutton et al, 1965). Figure 2 demonstrates the remarkable sensitivity of CNV and P300 components to the behavioral contingencies of a continuous performance task. CNV and P300 are clearly defined in hit trials, but are absent in miss trials.

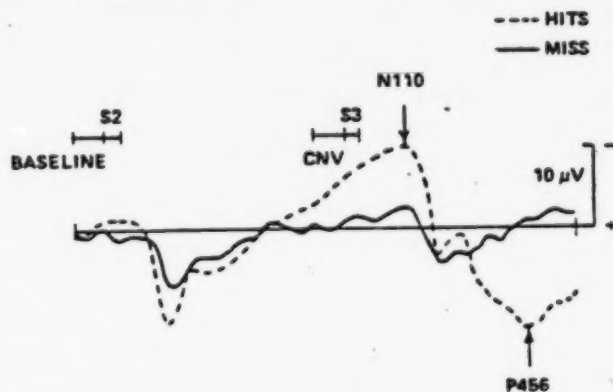


Fig. 2. Summary waveforms of hit and miss trials from seven subjects. The absence of CNV and P300 (labelled P456 in this example) during miss trials. (From Otto, 1977 p 10-23.)

SENSITIVITY OF ERSPs TO DRUGS AND TOXICANTS

Considerable evidence is available concerning the effects of psychotropic drugs on the CNV. The prospective sensitivity of ERSPs to toxicant substances may be inferred from the effects of commonly used psychotropic drugs. In general, CNV amplitude is enhanced by stimulants such as amphetamine (Kopell et al., 1974) and caffeine (Ashton et al., 1974) and decreased by depressants and tranquilizers and nitrazepam (Ashton et al., 1974). The divergent effects of stimulants and depressants on CNV amplitude are illustrated in fig. 3. In cases where the behavioral effects of drugs has been paradoxical, CNV changes have consistently mirrored behavioral observations. That is, when a given drug enhanced performance in some subjects, but depressed performance in others, CNV amplitude varied in the same direction as performance. Paradoxical effects have been reported with d-amphetamine (Tecce et al., 1974) and nicotine (Ashton et al., 1973). This evidence suggests that the CNV should provide a useful index of central-acting neurotoxicant effects.

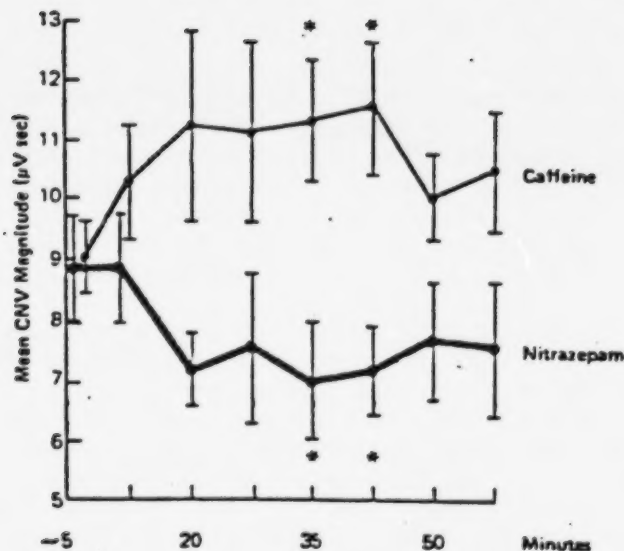


Fig. 3. Effect of stimulant (300 mg caffeine citrate, 13 subjects) and tranquilizer (2.5 mg nitrazepam, 12 subjects) drugs on CNV amplitude. Stimulants generally increase CNV amplitude, while depressants or tranquilizers usually decrease CNV amplitude. (Redrawn from Ashton et al, 1974).

Few efforts have been made to apply ERSP methods in neurotoxicological research. Groll-Knapp et al (1972) reported a dose-related decrease in CNV amplitude in subjects exposed to low concentrations of carbon monoxide, although the same laboratory (Groll-Knapp et al, 1978) was unable to replicate these results. Otto et al (1978) reported a paradoxical increase in CNV amplitude in subjects exposed to 100 ppm CO, but a decrease in subjects exposed to 200 ppm CO. P1 amplitude (following the CNV) increased proportional to CO exposure. These findings suggest a disinhibitory or excitatory effect on CNS function at low CO concentrations followed by the expected depressant effect at higher doses. Further study is required to clarify the extensive contradictions in reported neurobehavioral effects of low-level CO exposure.

A more convincing demonstration of the sensitivity of ERSPs to neurotoxicant exposure was recently reported by our laboratory (Otto et al., 1981). A linear relationship between slow wave voltage and blood lead level (figure 4) was observed in young children during sensory conditioning. Slow wave voltage varied systematically across the entire range of blood lead levels observed in these children (6-52 µg/dl) -- evidence that Pb exposure alters CNS function at levels considerably below the 30 µg/dl limit that is generally considered to be "safe" (CDC 1978). Although the functional significance of this finding is not clearly understood -- i.e., we cannot state with certainty that altered slow wave voltage reflects neural damage or even impaired sensory conditioning, the data indicate that this ERP parameter is extremely sensitive to body lead burden in children. Results of this work are reviewed in more detail elsewhere in the volume, (Otto et al.).

While the latter report provides encouraging evidence of the utility of ERP measures in neurotoxicology, ERSPs must be considered as experimental measures for several reasons. Although the relationships among ERSPs, behavior, and cognitive processes have been exhaustively explored during the past decade (cf. Otto 1978), very little is known

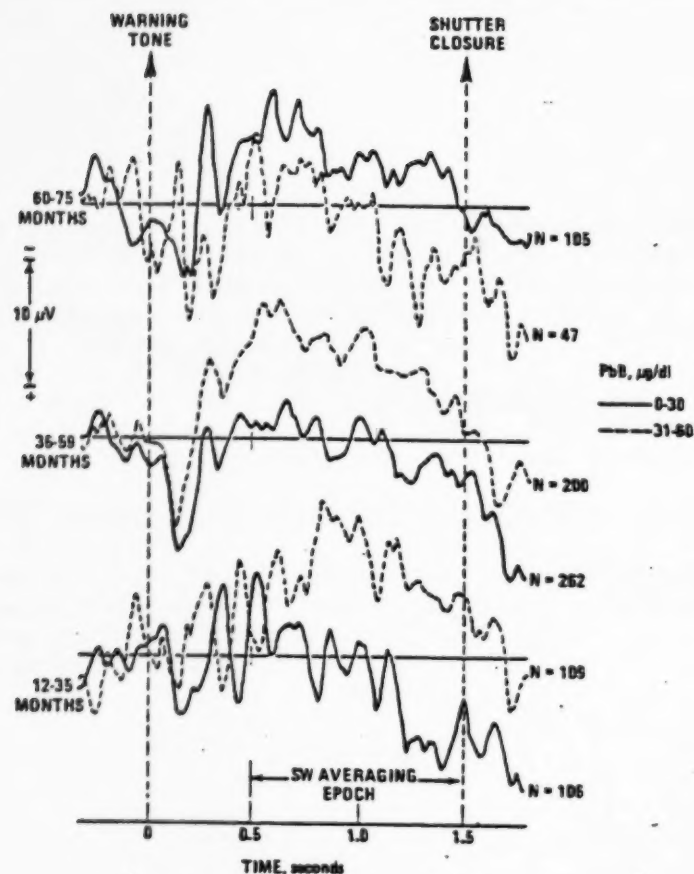


Fig. 4 Interactive effects of age and PbB levels on slow wave voltage during tone-shutter conditioning. Summary averages of all artifact-free trials were constructed for children in three age groups at two different PbB levels. N=number of trials included in average. (Redrawn from Otto et al., 1981).

about the anatomical, physiological, or chemical substrate of these intriguing waveforms. Even the psychological and behavioral significance of ERSPs remains a subject of lively debate. Little serious effort has been made to standardize testing paradigms or to construct population norms for any ERSP paradigm.

Other methodological problems limit the application of ERSP methods in occupational medicine. Eye and body movements produce considerable artifact during recording. Trials in which eye or body movements occur must be rejected from signal averages. Eye fixation on the stimulus generator is usually required to minimize eye movement artifact. The complexity and expense of computerized data acquisition and analysis systems also limit the application of ERSP methods.

EVALUATION OF NEUROTOXICITY MEASURES

Salient features and limitations of several event-related slow potentials that are promising experimental measures have been described. In order to compare the relative merits of different electrophysiological measures for neurotoxicological assessment of workers, a set of evaluation criteria must be specified. Twelve such criteria are listed and defined in Table I.

Neurotoxicity tests should meet the criteria required of psychometric tests -- i.e., each test should be valid, reliable, sensitive, and objective. Although not an essential requirement, tests should also be non-invasive and non-threatening, culture-free and as age-independent as possible. If the objective is population screening (as opposed to exhaustive clinical evaluation), three additional criteria should be considered in test evaluation. Tests should be rapid (as a rule of thumb, the battery should be limited to about 60 minutes in length -- that is only 8 subjects/day/ testing station), simple, and inexpensive.

TABLE I. EVALUATION CRITERIA FOR HUMAN NEUROTOXICITY TESTS

1. STANDARDIZED	standard procedures for test administration and measurement have been developed, published, and accepted by user community; normative data available for evaluation of clinical significance of data
2. VALID	test measures the dimension or function that it was selected to assess
3. RELIABLE	test provides comparable results when administered on repeated occasions
4. SENSITIVE	test discriminates between exposed and non-exposed populations; detects change at minimal effect threshold
5. OBJECTIVE	test provides a quantitative measure that is not susceptible to subjective bias
6. NON-INVASIVE	test does not require skin penetration
7. NON-THREATENING	test does not frighten or upset subject
8. AGE-INDEPENDENT	test scores do not vary with age
9. CULTURE-FREE	test scores do not vary with ethnic background or social class
10. RAPID	for population testing, individual measures should require no more than 10 minutes to administer; rapid scoring of response is also important
11. SIMPLE	test should be simple to administer and simple for the subject to perform
12. INEXPENSIVE	cost of test materials and scoring less than \$100

In Table II a simple binary rating scheme has been used to compare the relative merits of several ERSP measures and three sensory evoked potentials used widely in clinical neurology. The sensory measures are brainstem auditory (BAEP), pattern-reversal visual (PREP), and somatosensory (SEP) evoked potentials. Plus (+) indicates that the measure meets the criterion; minus (-) indicates that the measure does not; a question mark (?) indicates that insufficient evidence is available to assign a rating. While this rating scheme is crude and little evidence exists to evaluate the sensitivity or utility of these tests in populations exposed to industrial toxicants, Table II does provide a systematic basis to select appropriate electrophysiological measures for neurotoxicity assessment. Clinically validated tests of sensory dysfunction and non-specific demyelinating diseases (BAEP, PREP, and SEP) must be considered as prime candidates. Event-related slow potentials including the CNV and P300 have considerable promise, but require modification, standardization, and validation in order to meet many of the selection criteria for neurotoxicity testing in occupational medicine.

TABLE II. COMPARISON OF TESTS USED FOR NEUROTOXICITY ASSESSMENT

	BAEP	PREP	SEP	SW*	CNV	P300
(1) STANDARDIZED	+	+	+	-	-	-
(2) VALID	+	+	+	?	?	?
(3) RELIABLE	+	+	+	?	?	?
(4) SENSITIVE	+	+	+	+	?	?
(5) OBJECTIVE	+	+	+	+	+	+
(6) NON-INVASIVE	+	+	+	+	+	+
(7) NON-THREATENING	+	+	-	+	+	+
(8) AGE-INDEPENDENT	-	-	-	-	-	-
(9) CULTURE-FREE	+	+	+	-	?	?
(10) RAPID	+	+	+	-	+	+
(11) SIMPLE	+	+	-	-	-	-
(12) INEXPENSIVE	-	-	-	-	-	-

(*Slow wave voltage during sensory conditioning)

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